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Guest-Enhanced Kinetic Stability of Hydrogen-Bonded Dimeric Capsules of Tetraurea Calix[4]arenes

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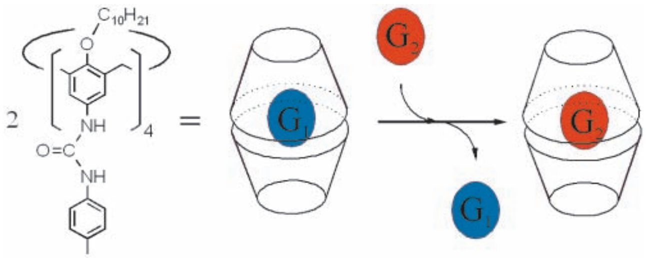
ABSTRACT



Inclusion complexes of self-assembled molecular dimers composed of two tetratolylurea calix[4]arenes show strongly different kinetic stability for different guests. In cyclohexane-d_{12}, half-life times for the exchange of a guest against the solvent vary from 2.9 h (chloroform) through 20 h (benzene) and 74 h (fluorobenzene) to 78 days for cyclohexane. This demonstrates that the kinetic stability of such a dimer can be strongly increased by the choice of a suitable guest.

Tetraurea derivatives of calix[4]arenes exist in nonpolar solvents as dimeric molecular capsules held together by a belt of 16 hydrogen bonds.[1] A suitable guest, often a solvent molecule, serves as a template of such an architecture. The structure of these dimers in the crystalline state was proved by X-ray analysis[2] and in solutions by NMR[3] and ESI-MS techniques.[4]

Despite the weak interactions involved in such dimeric structures, they are stable on the NMR time scale in solvents like benzene-d_6 (C_6D_6) and chloroform-*d* ($CDCl_3$). The rate constant of the guest exchange (benzene versus the solvent benzene) for a tetratolylurea calix[4]arene determined by EXSY spectroscopy is 0.47 s^{-1}.[3b] The kinetic stability of these structures can be drastically increased by the introduction of bulky groups at the urea functions[5] and also by the rigidification of the cone conformation.[6]

It is well-known that the solvent strongly influences the kinetic as well as the thermodynamic stability of such self-assembled systems. The (relative) thermodynamic stability of two types of hydrogen-bonded capsules was determined for different guests,[3a,7] but not much is known about the influence of the included guest on their kinetic stability.[8]

The tetratolylurea derivative **1**[4] (Figure 1) was chosen for a comparative study planned with 16 different organic guest

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[1] Rebek, J., Jr. *Chem. Commun.* **2000**, 637−643.

[2] Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. *Chem. Commun.* **1996**, 2533−2534.

[3] (a) Hamman, B. C.; Shimizu, K. D.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326−1329. (b) Mogck, O.; Pons, M.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, *119*, 5706−5712.

[4] Schalley, C. A.; Castellano, R. K.; Brody, M. S.; Rudkevich, D. M.; Siuzdak G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 4568−4579.

[5] Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 1264−1267.

[6] Rudkevich, D. M.; Böhmer, V.; Rebek, J., Jr.; et al., unpublished results.

[7] (a) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 9081−9082. (b) Chapman, R. G.; Olovsson, G.; Trotter, J.; Sherman, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 6252−6260.

[8] Recently, kinetic studies on a "tennis ball" and "soft ball" self-assembling molecular capsules were reported in the following: (a) Santamaria, J.; Martín, T.; Hilmersson, G.; Craig, S. L.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 8344−8347. (b) Rivera, J. M.; Craig, S. L.; Martín, T.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 2130−2132. (c) For theoretical calculations concerning this guest exchange, see: Wang, X.; Houk, K. N. *Org. Lett.* **1999**, *1*, 591−594.

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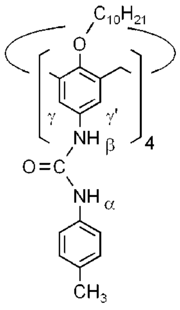

Figure 1. The tetraurea calix[4]arene **1** used in kinetic studies.

molecules. Their complexes were prepared by evaporation of a solution of **1** in these solvents. To determine their kinetic stability, cyclohexane-d_{12} was used as solvent (and new guest) since it does not compete with weak interactions such as hydrogen bonds or $\pi-\pi$ stacking interactions.[9] We encountered solubility problems for **1** in the fluorinated solvents trifluoromethylbenzene and 1,4-bis(trifluoromethyl)-benzene and for the complexes with iodobenzene, *p*-xylene, 1,4-dioxane, and cyclohexanone in cyclohexane-d_{12}, see Table 1.[10]

Table 1. Rate Constants for the Guest Escape (Exchange against C_6D_{12}) and Half-life Times of the Complexes of **1**·G·**1** with Some Organic Molecules[a]

guest	k, h^{-1}	$\tau_{1/2}$, h
cyclohexane	3.68×10^{-4}	1880
methylcyclohexane	3.89×10^{-4}	1780
benzene	3.44×10^{-2}	20
fluorobenzene	9.38×10^{-3}	74
1,4-difluorobenzene	4.71×10^{-4}	1470
chlorobenzene	1.74×10^{-2}	40
bromobenzene	3.04×10^{-2}	23
iodobenzene	*b*	
toluene	1.64×10^{-1}	4.2
p-xylene	*b*	
α,α,α-trifluorotoluene	*b, c*	
1,4-bis(trifluoromethyl)benzene	*c*	
chloroform	2.36×10^{-1}	2.9
tetrachloromethane	3.17×10^{-4}	1120
1,4-dioxane	*b*	
cyclohexanone	*b*	

[a] The rate constants are the average from three kinetic runs and show standard deviations ≤±10%.[14] [b] Complex **1**·G·**1** not soluble in cyclohexane. [c] **1** is not soluble in an excess of the guest G.

The guest escape (or better exchange) from the dimeric capsule was followed by ^{1}H NMR at 25 °C monitoring the signal intensities of the included guest or an appropriate signal of the host in the old or new complex. A typical set of spectra thus obtained is presented in Figure 2 and typical first-order kinetic plots for different guests are presented in Figure 3. The rate constants for the reaction $\mathbf{1}\cdot G\cdot\mathbf{1} + C_6D_{12} \rightarrow \mathbf{1}\cdot C_6D_{12}\cdot\mathbf{1} + G$ are summarized also in Table 1.

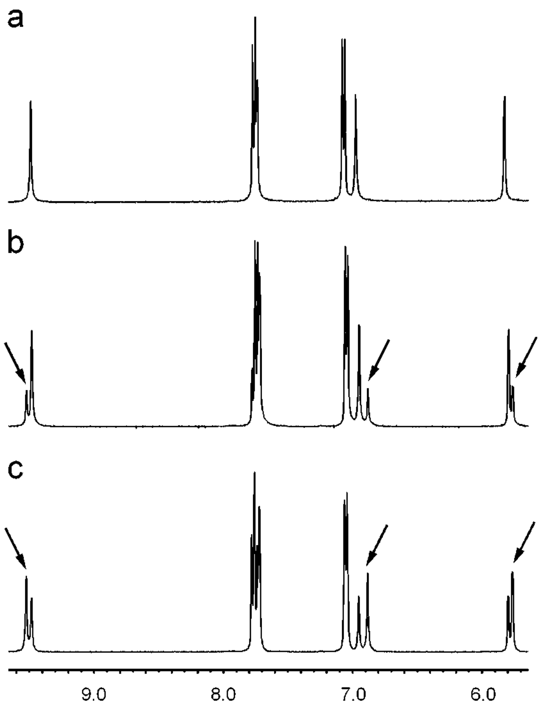

Figure 2. ^{1}H NMR spectra of $\mathbf{1\cdot CCl_4\cdot 1}$ (C_6D_{12}, 400 MHz, 25 °C) after (a) 15 min, (b) 26 days, and (c) 70 days. Some signals of the $\mathbf{1\cdot C_6D_{12}\cdot 1}$ complex are indicated by an arrow.

Not necessarily expected in this size, the rate for the escape of benzene from its complex with **1** is lower by almost 5 orders of magnitude in cyclohexane-d_{12} in comparison to that in benzene-d_6.[3b,11] The escape of toluene is faster than the escape of benzene (Table 1), which probably reflects its less favorable steric fit into the dimer. On the other hand, the cyclohexane complex is 2 orders of magnitude more stable

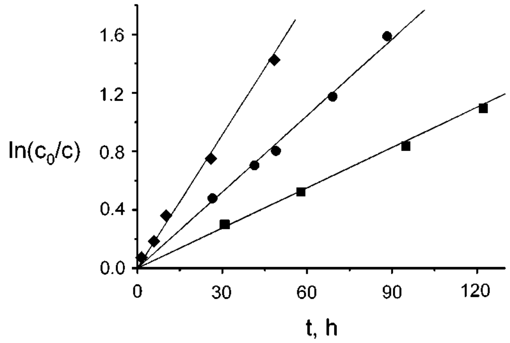

Figure 3. First-order plots for the disappearance of the signals of $\mathbf{1}\cdot C_6D_5F\cdot\mathbf{1}$ (■), $\mathbf{1}\cdot C_6D_5Cl\cdot\mathbf{1}$ (●), and $\mathbf{1}\cdot C_6D_5Br\cdot\mathbf{1}$ (◆) (C_6D_{12}, 400 MHz, 25 °C).

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(9) Rheichart, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, 1990.

Table 2. Chemical Shifts of the Protons α−γ′ (^{1}H NMR) and Complexation-Induced Shifts (CIS) of the Guest in **1**·G·**1** Complex[a]

guest	α	β	γ	γ′	CIS values of the included guest[b]
cyclohexane	9.53	6.88	7.72	5.76	−2.88 (s)
methylcyclohexane	9.56	6.51	7.75	5.63	−2.69 (d, 3H), −1.82 (m, 1H), −2.70 (m, 2H), −2.52 (m, 2H), −2.99 (m, 6H)
1,4-difluorobenzene	9.49	6.71	7.64	5.78	−4.05 (t)[c]
benzene	9.44	6.75	7.62	5.76	−3.34 (s)
fluorobenzene	9.45	6.73	7.63	5.78	−1.95 (t, 1H), −4.08 (dt, 2H),[c] −4.03 (t, 2H)[c]
chlorobenzene	9.45	6.44	7.61	5.68	−1.77 (t, 1H), −3.84 (t, 2H), −3.99 (d, 2H)
bromobenzene	9.42	6.30	7.62	5.64	−1.63 (t, 1H), −3.78 (t, 2H), −3.95 (d, 2H)
toluene	9.48	6.35	7.66	5.64	−3.17 (t, 1H), −3.29 (t, 2H), −3.03 (d, 2H); −3.12 (s, 3H)
chloroform	9.49	7.04−7.06[d]	7.68	5.86	−2.59 (s)
tetrachloromethane	9.48	6.95	7.72	5.79	

[a] Chemical shifts are given as δ values in ppm; spectra were recorded in cyclohexane-d_{12} solutions. For the description of the protons α−γ′, see Figure 1. [b] CIS = $\delta_{\text{observed}} - \delta_{\text{free}}$. [c] Due to the ^{1}H−^{19}F coupling. [d] The signal is overlapped with the doublet of the tolyl group.

than the benzene complex and there is almost no difference between the stabilities of the cyclohexane and methylcyclohexane complexes. Surprisingly, the complexes of benzene and bromobenzene possess a similar stability,[12] while there is a slight decrease in going from fluoro- via chloro- to bromobenzene.[13] The stability is significantly increased from 20 to 74 and finally to 1470 h ($\tau_{1/2}$) from benzene to fluorobenzene and to 1,4-difluorobenzene.

Another interesting guest pair is chloroform and tetrachloromethane. Their complexes (Table 1) again show very different stability, which might be explained either by a better fit of CCl_4 or by the relatively acidic CH present in the chloroform molecule which makes it possible to “unzip” the dimer from inside by interaction with the urea functions.[15,16]

In Table 2 the chemical shifts for various protons of the capsule are shown together with complexation-induced values of the guest. While the α-proton, representing the strongest hydrogen bond, varies only by 0.14 ppm the weaker hydrogen-bonded β-proton is most sensitive ($\Delta\delta = 0.75$ ppm) to the nature of the included guest. The aromatic protons γ and γ′ vary by 0.14 and 0.23 ppm, respectively.

It is tempting to correlate the kinetic stability of the different complexes with the strength of this weaker hydrogen bond[2] (as expressed by the chemical shift of β, see Figure 4). In fact, δ decreases by 0.43 ppm in going from fluoro- to bromobenzene and is higher by 0.4 ppm for benzene in comparison with toluene as guest.[17] On the other hand, there is nearly no difference in β shifts for 1,4-difluorobenzene, fluorobenzene, and benzene, which form complexes with quite different stabilities, and the kinetically most labile complex with chloroform shows even the highest chemical shift for β.

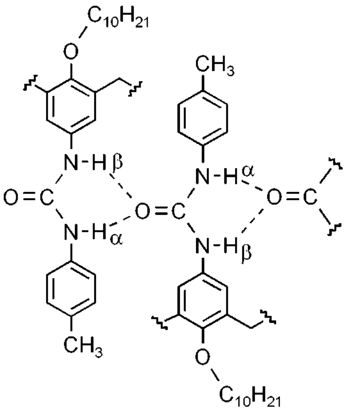

Figure 4. Schematic representation of two types of hydrogen bonds present in a dimer.[2]

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(10) It is noteworthy that the solubility of the complexes listed in Table 1 depends drastically on the included guest. For example, the chloroform and toluene complexes are much less soluble (<1 mg in 0.8 mL) than the kinetically more stable ones; compare the different chromatographic properties observed for hemicarceplexes which differ only by the guest molecules: Park, B. S.; Knobler, C. B.; Eid, C. N., Jr.; Warmuth, R.; Cram, D. J. *Chem. Commun.* **1998**, 55−56. Yoon, J.; Cram, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11796−11806.

(11) For this comparison we assume that the ether residues have no significant influence on the rate of guest exchange.

(12) This observation does not fit well to the 55% occupancy of the capsule interior proposed by Mecozzi, S.; Rebek, J., Jr. *Chem. Eur. J.* **1998**, *4*, 1016−1022.

(13) The relative thermodynamic stability of a similar tetraurea with monosubstituted benzene molecules (in xylene-d_{10}) is the following: F > H > Cl > CH_3, see ref 3a.

(14) The cyclohexane-d_{12} (99.5%) used for kinetic studies was purchased from Deutero GmbH and was kept over 4 Å molecular sieves. A sample of **1** for kinetic measurements was prepared by stirring its solution in dichloromethane and methanol (5−10%) with basic aluminium oxide (20-fold excess) for 1.5 h. After filtration, evaporation under reduced pressure to 10% of the initial volume, and precipitation with methanol (p.a.), **1** was dried in a vacuum for 6 h at 100 °C and finally kept in a desiccator over phosphorus pentoxide and potassium hydroxide. Complexes were prepared by dissolving **1** in a large excess of the guest, evaporating the solution, and drying the residue in a vacuum. All complexes were then kept in a desiccator over phosphorus pentoxide and potassium hydroxide. The kinetic runs were performed in NMR tubes in the presence of two pieces of molecular sieves at 2−10 mM concentration of the complexes (0.2−0.5 mM in the case of $CHCl_3$ and toluene as guest). All spectra were recorded on a Bruker DRX 400 instrument using a proton-sensitive probehead.

(15) For the ability of chloroform to form hydrogen bonds, see, for instance: Wiley, G. R.; Miller, S. I. *J. Am. Chem. Soc.* **1972**, *94*, 3287−3293.

(16) Addition of 0.1% C_6D_6, a potential impurity in cyclohexane-d_{12}, led to an increase of the reaction rate by a factor of 2−3. All the results reported were obtained with the same batch of cyclohexane-d_{12}.

(17) The CIS values for the *para*-proton change from −1.95 to −1.63 ppm from fluoro- to bromobenzene, while a value of −3.17 ppm for toluene suggests a rather different orientation of the included guest, compare 3a.

In conclusion, there is no doubt that the molecule included within the cavity is a supramolecular tool which can drastically increase the kinetic stability of self-assembled capsules by nearly 3 orders of magnitude. If the solvent is simultaneously taken as guest, the kinetic stability increases by more than 6 orders of magnitude in going from benzene to cyclohexane. A general explanation for the drastic differences must consider various factors such as sterical fit, polarity, H-bonding ability, etc. and will be given in a forthcoming full paper.

Further measurements[18] will include additional potential guest molecules as well as urea derivatives, providing better solubility in cyclohexane. In addition, we will extend these studies also to other solvents, hoping to establish a more detailed mechanistic picture for the guest exchange.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (Bo523/14-1) and the Fonds der Chemischen Industrie. We are grateful to Prof. Dr. J. Okuda, giving us generous access to the NMR facilities, to Dr. B. Mathiasch for technical assistance in running the NMR instrument, and to Dr. C. Schmidt for helpful discussions.

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(18) Recently fluorescence resonance energy transfer has been used to characterize the kinetic stability: Castellano, R. K.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 7876−7882.